(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 428 296 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification : **08.06.94 Bulletin 94/23**

(51) Int. Cl.[5] : **A61K 33/12,** A61K 31/80, // (A61K31/695, 31:445, 31:235), (A61K31/765, 31:695), (A61K33/12, 31:695)

(21) Application number : **90311930.3**

(22) Date of filing : **31.10.90**

(54) **Pharmaceutical compositions for treating gastrointestinal distress.**

(30) Priority : **01.11.89 US 430707**

(43) Date of publication of application : **22.05.91 Bulletin 91/21**

(45) Publication of the grant of the patent : **08.06.94 Bulletin 94/23**

(84) Designated Contracting States : **AT BE CH DE ES FR GB IT LI**

(56) References cited :
FR-A- 2 565 107
GB-A- 1 097 955
US-A- 2 951 011
US-A- 4 786 502

(56) References cited :
Annals of Internal Medicine 1986, vol. 105(1) pp. 61-62, Naresh K. et al."Activated Charcoal, Simethicone and Intestinal Gas: A double-blind study"

(73) Proprietor : **McNEIL-PPC, INC.**
Van Liew Avenue
Milltown New Jersey 08850 (US)

(72) Inventor : **Garwin, Jeffrey L.**
135 Fennerton Road
Paoli, PA 19301 (US)

(74) Representative : **Mercer, Christopher Paul et al**
Carpmaels & Ransford
43, Bloomsbury Square
London WC1A 2RA (GB)

EP 0 428 296 B1

Description

This invention relates to a pharmaceutical composition for treating gastrointestinal distress comprising an effective amount of an antidiarrheal compound and an antiflatulent effective amount of simethicone and to its use.

Gastrointestinal distress for the purposes of the present invention is defined as discomfort associated with an intestinal disorder characterized by symptoms of diarrhea and flatulence or gas. Diarrhea is the abnormally frequent passage of watery stool.

Diarrhea may have a variety of causes including bacteria or viral induced diarrhea. Travelers diarrhea, for example, is also believed to be of microbial origin. Diarrhea may also be a side effect of drug administration, particularly antibiotics. Diarrhea may be induced by food intolerance which is caused by allergy or the ingestion of foods that are excessively fatty, spicy, or contain a high degree of fermentable carbohydrate, roughage or a large number of seeds. Food intolerance may also be brought on by a performed toxin in the food thus causing food poisoning. Other conditions and diseases can also cause diarrhea, and diarrhea may only be one of many symptoms associated with a major illness.

Diarrhea is thus a symptom of an intestinal disorder or other bodily function and symptomatic relief can be accomplished by the use of various prescription and nonprescription products. The active ingredients in these products include loperamide, attapulgite, bismuth subsalicylate, diphenoxylate HCl, polycarbophil, calcium polycarbophil and mixtures thereof.

Flatulence or intestinal gas is another intestinal disorder which contributes to gastrointestinal distress. Such gas exists as trapped gas bubbles which manifest feelings of pain, bloating and cramping in the abdominal area. It has been surprisingly found in a study of people complaining of diarrhea that about 67% of the population study also complained of accompanying gas.

FR-A-2565107 describes medicaments containing activated carbon for use in treating gastrointestinal disorders. The medicaments comprise activated carbon particles bound in a pharmaceutically acceptable matrix such as an acrylic resin. The matrix dissolves in the gastrointestinal tract to release the activated carbon. With a suitable choice of matrix material the activated carbon can be selectively released in the intestine, where it is effective to relieve diarrhea and flatulence. Preferably, the medicaments comprise a central core coated with one or more layers of the matrix material containing activated carbon. There may also be additional layers of matrix materials containing particles of additional active substances, such as aluminium hydroxide, magnesium hydroxide, attapulgite or simethicone.

US-A-2951011 describes therapeutic compositions for the administration of organopolysiloxanes for the relief of flatulence. The compositions comprise particulate antacid material, the particles of which are coated with a non-toxic organopolysiloxane, such as simethicone.

While various products exist for separately treating diarrhea and gas, no product has heretofore been proposed for treating the combination of the symptoms of both diarrhea and gas which has been defined herein as gastrointestinal distress. It is therefore an object of the present invention to provide a composition for the treatment of gastrointestinal distress in response to a long felt need which has now been recognized by the above-mentioned study.

The foregoing object of fulfilling a long felt need for a pharmaceutical composition which can relieve the symptoms of gastrointestinal distress, i.e. diarrhea and flatulence has now been accomplished in accordance with the compositions and methods of the present invention.

In accordance with the purposes of the invention as embodied and fully described herein, the invention comprises a pharmaceutical composition for treating gastrointestinal distress comprising an effective amount of an antidiarrheal compound and an antiflatulent effective amount of simethicone. The antidiarrheal compound is selected from the group consisting of loperamide, attapulgite, diphenoxylate, polycarbophil, calcium polycarbophil and pharmaceutically acceptable salts thereof or mixtures thereof. In preferred embodiments the antidiarrheal compound is loperamide.

The composition according to the present invention may be used for treating gastrointestinal distress comprising administering a combination pharmaceutical composition to a patient comprising an effective amount of an antidiarrheal compound and an antiflatulent effective amount of simethicone. The antidiarrheal compound is selected from those described above with loperamide being particularly preferred.

Reference will now be made in detail to preferred embodiments of the invention, examples of which are illustrated in the following examples section.

To achieve the object of the invention of providing a pharmaceutical composition for treating gastrointestinal distress, an effective amount of an antidiarrheal composition is combined with an antiflatulent effective amount of simethicone.

The preferred antiflatulent compound combined with effective amounts of an antidiarrheal compound in

accordance with the invention is simethicone, also known as polydimethylsiloxane. Simethicone is a surface active agent which acts as a defoamer or dispersent of gas bubbles by changing the surface tension of the bubbles to enable them to coalesce. The defoaming action of simethicone relieves flatulence by dispersing and preventing the formation of mucous surrounded gas pockets in the gastrointestinal tract. By reducing the size of the gas bubbles, the gas is free to travel through the gastrointestinal tract for release by belching or passing flatus. This release thus relieves the pain and pressure commonly associated with the presence of gas in the gastrointestinal tract.

Simethicone acts largely in the stomach but is also believed to have gas relieving effect in the intestines. Since simethicone is not absorbed or metabolized by the body, if released in the stomach area, it will proceed through the gastrointestinal tract into the intestines. In preferred embodiments of the composition of the invention, simethicone is presented in an immediate release form that is released in the stomach area. Enteric coated simethicones or a combination of immediate release and enteric coated simethicones may be included in accordance with the present invention to release the simethicone in the intestines.

The preferred dosage ranges for simethicone is in the range of about 20 to 125 mg. per dosage unit, generally not to exceed 500 mg/day. The dosage ranges may vary for age and weight of a patient as well as the severity of symptoms.

Effective amount of antidiarrheal compounds combined with effective amounts of simethicone vary with the particular antidiarrheal compounds selected. The antidiarrheal compounds and their preferred dosage ranges as a component of the composition in accordance with the invention are as follows: loperamide with a dosage range from 0.5 mg to 8.0 mg; attapulgite with a dosage range from 300 mg to 1600 mg; diphenoxylate HCl with a preferred dosage range from 0.7 mg to 10 mg; polycarbophil with a preferred dosage range of 150 to 2000 mg.; and calcium polycarbophil with a preferred dosage range of 150 to 2000 mg. Compatible mixtures of these antidiarrheal compounds and their pharmaceutically acceptable salts can also be included in a pharmaceutical composition of the invention.

Loperamide is the preferred antidiarrheal active for use in the pharmaceutical composition of the invention. Loperamide as a component of the present invention includes pharmaceutically acceptable salts of loperamide such as loperamide HCl. Loperamide acts by slowing intestinal motility and by normalizing water and electrolyte movement through the bowel. Further, loperamide inhibits peristaltic activity by a direct effect on circular and longitudinal muscles of the intestinal walls. Loperamide in man thus prolongs the transit time of the intestinal contents and reduces the daily fecal volume and increases the viscosity and bulk density and thus diminishes loss of food and electrolytes.

Dosage ranges chosen for the loperamide component of the composition of the present invention depend upon the age and weight of the patient. A preferred adult dose given initially for the treatment of gastrointestinal distress is 4 mg followed by 2 mg after each unformed stool until diarrhea is controlled. A preferred ratio of simethicone to loperamide is in the range of from about 100 to 1 to about 10 to 1. Loperamide acts in the intestines and is therefore preferably enteric coated so that it will pass through the stomach and be released in the small intestines. While enteric coating is preferred, it is not essential since loperamide will not be absorbed or metabolized in the stomach but will eventually pass through into the small intestines in any event.

Other ingredients both active and inactive can be added to the combination antidiarrheal/antiflatulence compositions of the invention. For example, flavoring compositions are desirably added to chewable and liquid dosage forms. The composition of the invention can also be provided in an oral solid dosage form.

Antispasmodic and anticholinergic compositions and their pharmaceutically acceptable salts may, for example, be added to the compositions of the invention. Examples of antispasmodics include phenobarbital, dicyclomine HCl, belladonna alkaloids, and atropine. Further, various digestive enzymes such as lipase, amylase and protease may also be provided as additional components in combination with the compositions of the invention to reduce and relieve gastrointestinal distress.

Compositions according to the present invention are used for of treating gastrointestinal distress. The method comprises administering a combination pharmaceutical composition in accordance with the invention to a patient having the symptoms of gastrointestinal distress which is a combination of diarrhea and flatulence, including discomforts associated with flatulence which may include bloating, pain, and uncomfortable fullness. The use comprises treating the patient with an effective amount of an antidiarrheal composition and an antiflatulent effective amount of simethicone. The antidiarrheal is selected from the group consisting of loperamide, attapulgite, diphenoxylate, polycarbophil, calcium polycarbophil and mixtures thereof. More preferably, the antidiarrheal composition is loperamide in a dosage range of about 0.5 to 8.0 mg combined with from about 20 to 125 mg of simethicone.

Examples

Example I. Bi-layer Loperamide HCl 2 mg/Simethicone 80 mg, Chewable Tablet

Ingredients		mg/tablet
SIMETHICONE LAYER		
dicalcium phosphate, NF		784.000
collodial silicon dioxide, NF		40.000
simethicone, USP		80.000
aspartame, NF		5.000
flavors		16.056
stearic acid, NF		18.879
	Layer Total	943.935
LOPERAMIDE LAYER		
loperamide HCl, USP		2.000
sucrose, NF		12.000
mannitol, USP		565.120
aspartame, NF		2.820
flavors		9.060
stearic acid, NF		6.000
colloidal silicon dioxide, NF		3.000
	Layer Total	600.000
Bi-layer Tablet	Total	1541.935

Manufacturing Instructions

A. Simethicone Granulation

Combine dicalcium phosphate, colloidal silicon dioxide, simethicone, aspartame, flavors and stearic acid. Mix using an appropriate mixer (e.g., PK Blender) for 10 minutes.

B. Loperamide Granulation

Granulate loperamide HCl with sucrose and a portion of the mannitol using an appropriate fluid bed granulator (e.g., Glatt GPCG-3).

Dry blend stearic acid, colloidal silicon dioxide, aspartame, flavors and the remaining mannitol with the above granulation. Mix for 10 minutes in an appropriate mixer (e.g., PK Blender).

C. Compression

Compress the loperamide and simethicone granulations as separate layers using a bi-layer tablet press (e.g., Stokes Versa Press).

Example II. Bi-layer Loperamide HCl 2 mg./Simethicone 80mg. Swallowable Caplet

Ingredients		mg/tab
SIMETHICONE LAYER		
dicalcium phosphate, NF		784.000
collodial silicon dioxide, NF		40.000
simethicone, USP		80.000
sodium starch glycolate, NF		80.360
stearic acid, NF		20.090
	Layer Total	1004.450
LOPERAMIDE LAYER		
loperamide HCl, USP		2.000
mannitol, USP		101.000
sucrose, NF		12.000
microcrystalline cellulose, NF		6.460
sodium starch glycolate, NF		3.880
stearic acid, NF		1.290
colloidal silicon dioxide, NF		0.646
	Layer Total	129.276
Bi-layer Caplet	Total	1133.7260

Manufacturing Instructions

A. Simethicone Granulation

Combine dicalcium phosphate, colloidal silicon dioxide, simethicone, sodium starch glycolate and stearic acid. Mix using an appropriate mixer (e.g., PK Blender) for 10 minutes.

B. Loperamide Granulation

Granulate loperamide HCl with sucrose and a portion of the mannitol using an appropriate fluid bed granulator (e.g., Glatt GPCG-3).

Dry blend stearic acid, colloidal silicon dioxide, microcrystalline cellulose land sodium starch glycolate with the above granulation and mix for 10 minutes using an appropriate mixer (e.g., PK Blender).

C. Compression

Compress the loperamide and simethicone granulations as separate layers using an appropriate bi-layer tablet press (e.g., Stokes Versa Press).

Example III. Loperamide 2 mg./Simethicone 80 mg. Emulsion

Ingredients	mg/tab
sucrose, NF	35.00
sorbitol, USP (70%)	20.00
sodium benzoate, NF	0.10
benzoic acid, USP	0.10
citric acid, USP (Anydrous)	0.032
propylene glycol, USP	15.00
glycerin, USP	15.00
carboxy polymethylene, NF	0.20
loperamide HCl, USP	0.02
30% simethicone emulsion	0.80
10% sodium hydroxide solution	0.80
purified water, USP, qs to:	100.00 ml

Manufacturing Instructions

Combine the above ingredients (except 10% sodium hydroxide solution) with mixing.
Add with gentle mixing, 10% sodium hydroxide solution.
QS to final volume with purified water and mix (e.g. IKA-Werk mixer at low speed).

Example IV. Loperamide 2mg/Bismuth Subsalicylate 300 mg/Simethicone 80 mg Emulsion/Suspension

Example IV is carried out using the same ingredients and procedure as used for the emulsion of Example III except that 3.00 gm bismuth subsalicylate is added to the emulsion.

Use in Treating Patients with Gastrointestinal Distress

A patient exhibiting the symptoms of gastrointestinal distress, i.e. diarrhea and excess gas or flatulence, is treated by the administration of two caplets of the loperamide/simethicone composition in accordance with Example II whereby each caplet contains 2 mg of loperamide and 80 mg of simethicone as an initial dose followed by administering an additional caplet after each unformed stool not to exceed 8 mg loperamide per day (4 caplets), one caplet being a dosage of 2 mg. of loperamide and 80 mg. of simethicone.

The combined antidiarrheal and antiflatulent compositions of the invention may be provided in a sustained release formulation for treatment of chronic gastrointestinal distress.

Claims

1. A pharmaceutical composition comprising an effective amount of an antidiarrheal compound selected from the group consisting of loperamide, attapulgite, diphenoxylate, polycarbophil, calcium polycarbophil, a pharmaceutically acceptable salt thereof or a mixture thereof and an antiflatulent effective amount of simethicone.

2. The composition of claim 1 wherein the antiflatulent effective amount of simethicone is in the range of 20 to 125 mg per dose and the amount of the antidiarrheal compound is 0.5 to 8.0 mg of loperamide; 300 mg to 1600 mg of attapulgite; 0.7 mg to 10 mg of diphenoxylate HCl; 150 mg to 2000 mg of polycarbophil; 150 to 2000 mg of calcium polycarbophil per dose, or a pharmaceutically acceptable salt thereof.

3. The composition of any one of claims 1 and 2 comprising an antidiarrheal effective amount of loperamide and an antiflatulent effective amount of simethicone.

4. The composition of claim 3 wherein the ratio of simethicone to loperamide is in the range 100:1 to 10:1.

5. The composition of claim 3 or claim 4 wherein the antidiarrheal effective amount of loperamide is in the range 0.5 to 8.0 mg per dose and the antiflatulent amount of simethicone is 20 to 125 mg of simethicone per dose.

6. The composition of claim 5 wherein the amount of loperamide is 2 mg per dose and the amount of simethicone is 80 mg per dose.

7. The composition of any one of claims 1 to 6 wherein the pharmaceutical composition is in an oral solid dosage form, a liquid dosage form or a chewable dosage form.

8. Use of a composition according to any one of claims 1 to 7 for the preparation of a medicament for treating an intestinal disorder characterized by the symptoms of diarrhea and flatulence or gas.

9. A method of producing a composition according to any one of claims 1 to 7 which comprises forming a pharmaceutical composition containing an effective amount of an antidiarrheal compound selected from the group consisting of loperamide, attapulgite, diphenoxylate HCl, polycarbophil, calcium polycarbophil, a pharmaceutically acceptable salt thereof or a mixture thereof and an antiflatulent effective amount of simethicone.

Patentansprüche

1. Pharmazeutische Zusammensetzung, umfassend eine wirksame Menge einer antidiarrhoischen Verbindung, ausgewählt aus der Gruppe bestehend aus Loperamid, Attapulgit, Diphenoxylat, Polycarbophil, Calciumpolycarbophil, einem pharmazeutisch verträglichen Salz davon oder einem Gemisch davon und einer gegen Blähungen wirksamen Menge Simethicon.

2. Zusammensetzung nach Anspruch 1, in der die gegen Blähungen wirksame Menge Simethicon im Bereich von 20 bis 125 mg pro Dosis liegt und die Menge der antidiarrhoischen Verbindung 0,5 bis 8,0 mg Loperamid; 300 mg bis 1600 mg Attapulgit; 0,7 mg bis 10 mg Diphenoxylat HCl; 150 mg bis 2000 mg Polycarbophil; 150 bis 2000 mg Calciumpolycarbophil pro Dosis beträgt, oder ein pharmazeutisch verträgliches Salz davon.

3. Zusammensetzung nach einem der Ansprüche 1 und 2, umfassend eine antidiarrhoisch wirksame Menge Loperamid und eine gegen Blähungen wirksame Menge Simethicon.

4. Zusammensetzung nach Anspruch 3, in der das Verhältnis von Simethicon zu Loperamid im Bereich 100:1 bis 10:1 liegt.

5. Zusammensetzung nach Anspruch 3 oder Anspruch 4, in der die antidiarrhoisch wirksame Menge Loperamid im Bereich 0,5 bis 8,0 mg pro Dosis liegt und die gegen Blähungen wirksame Menge Simethicon 20 bis 125 mg Simethicon pro Dosis beträgt.

6. Zusammensetzung nach Anspruch 5, in der die Menge Loperamid 2 mg pro Dosis beträgt und die Menge Simethicon 80 mg pro Dosis beträgt.

7. Zusammensetzung nach einem der Ansprüche 1 bis 6, in der die pharmazeutische Zusammensetzung in einer oralen festen Dosierungsform, einer flüssigen Dosierungsform oder einer kaubaren Dosierungsform vorliegt.

8. Verwendung einer Zusammensetzung nach einem der Ansprüche 1 bis 7 zur Herstellung eines Medikaments zur Behandlung einer intestinalen Störung, die durch die Symptome von Diarrhoe und Blähungen oder Gas gekennzeichnet ist.

9. Verfahren zur Herstellung einer Zusammensetzung nach einem der Ansprüche 1 bis 7, das das Bilden

einer pharmazeutischen Zusammensetzung umfaßt, die eine wirksame Menge einer antidiarrhoischen Verbindung, ausgewählt aus der Gruppe bestehend aus Loperamid, Attapulgit, Diphenoxylat HCl, Polycarbophil, Calciumpolycarbophil, einem pharmazeutisch verträglichen Salz davon oder einem Gemisch davon und eine gegen Blähungen wirksame Menge Simethicon enthält.

Revendications

1. Composition pharmaceutique comprenant une quantité efficace d'un composant antidiarrhéique sélectionné dans le groupe consistant en lopéramide, attapulgite, diphénoxylate, polycarbophil, polycarbophil calcium, leurs sels acceptables en pharmacie ou leurs mélanges ainsi qu'une quantité antiflatulente efficace de siméthicone.

2. Composition de la revendication 1 où la quantité antiflatulente efficace de siméthicone est comprise entre 20 et 125 mg par dose et la quantité du composant antidiarrhéique est comprise entre 0,5 et 8,0 mg de lopéramide ; 300 mg et 1600 mg d'attapulgite ; 0,7 mg et 10 mg de HCl diphénoxylate ; 150 mg et 2000 mg de polycarbophil ; 150 et 2000 mg de polycarbophil calcium par dose, ou bien un sel acceptable en pharmacie.

3. Composition selon l'une quelconque des revendications 1 et 2 comprenant une quantité antidiarrhéique efficace de lopéramide et une quantité antiflatulente efficace de siméthicone.

4. Composition de la revendication 3 où le rapport de siméthicone à lopéramide est compris entre 100:1 et 10:1.

5. Composition de la revendication 3 ou de la revendication 4 où la quantité antidiarrhéique efficace de lopéramide est comprise entre 0,5 et 8,0 mg par dose et la quantité antiflatulente de siméthicone est de 20 à 125 mg de siméthicone par dose.

6. Composition de la revendication 5 où la quantité de lopéramide est de 2 mg par dose et la quantité de siméthicone est de 80 mg par dose.

7. Composition selon l'une quelconque des revendications 1 à 6 où la composition pharmaceutique est une forme de dose solide orale, une forme de dose liquide ou une forme de dose masticable.

8. Utilisation d'une composition selon l'une quelconque des revendications 1 à 7 pour la préparation d'un médicament pour le traitement d'un trouble intestinal, caractérisée par les symptômes de la diarrhée et de la flatulence ou des gaz.

9. Méthode de production d'une composition selon l'une quelconque des revendications 1 à 7 qui consiste à former une composition pharmaceutique contenant une quantité efficace d'un composant antidiarrhéique sélectionné dans le groupe consistant en lopéramide, attapulgite, HCl diphénoxylate, polycarbophil, polycarbophil calcium, leurs sels acceptables en pharmacie ou leurs mélanges et une quantité antiflatulente efficace de siméthicone.